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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,918	12/28/2001	Rajiv Shah	047711-0293	2208

7590 03/10/2009

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ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
03/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/035,918
Filing Date: December 28, 2001
Appellant(s): SHAH ET AL.

Ted R. Rittmaster
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 23, 2008 appealing from the Office action mailed June 27, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

10/715,143. This application is currently under Appeal (Appeal Brief filed on November 26, 2008) and is a divisional of the instant application.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Valdes, T.I. "In Vitro and In Vivo Degradation of Glucose Oxidase Enzyme Used for an Implantable Glucose Biosensor" Diabetes Technology & Therapeutics, vol2, no. 3 (Nov 3, 2000), pp. 367-376.

Cherry J.R. "Directed Evolution of a Funal Peroxidase" Nature Biotechnology, vol17 (Apr , 1999), pp. 379-384.

Hatzinikolaou, D.G. "A New Glucose Oxidase from Aspergillus niger: Characterization and Regulation Studies of Enzyme and Gene" Appl. Microbiol. Biotechnol, vol46, no. 4 (Nov, 1996), pp. 371-381.

MISONIX - Cole Parmer Catalog.

EP 0 251 475 A1	Wagner	5-1987
6,689,265	Heller	2-2004

Aldrich Catalog, 1998-1999, page 1005.

Yin, L. "Glucose ENFET Doped with MnO2 Poweder" Sensors and Actuators B, vol76 (2001), pp. 187-192.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 12-15, 18-24 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Cherry et al. and Hatzinikolaou et al.

Claims 1, 3-5, 12-15, 18-24 and 44-45 are drawn to a method of formulating or producing mutant glucose oxidases by obtaining a library of glucose oxidase genes, creating a library of mutated glucose oxidase genes by the methods recited in claims 20-24, introducing each mutated glucose oxidase genes into separate expression vectors, inserting said vectors into host organisms recited in claim 19, growing colonies of the host organism, determining whether the colonies contain active glucose oxidase by the methods recited in claims 3-5, 12-15, 18-24 and 44-45 and determining whether the colonies are resistant to peroxide and then measuring the concentration of the glucose oxidase.

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Valdes et al. (cited previously on form PTO-892) discloses that glucose oxidase in glucose sensors are degraded/deactivated by peroxide, a by-product of the oxidation of glucose by glucose oxidase, and this "decay can lead to the eventual failure of the senor" (abstract and pages 367-368). Valdes et al. teaches that to ensure longer sensor functionality, instead of replacing the sensor with fresh enzyme, as has been practiced in the art, techniques to "prevent the degradation of the enzyme" is advantageous (page 375). With this teaching at hand, one having ordinary skill in the art would conclude that deactivation of glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as discussed below. Valdes et al. also teaches a method of determining activity of glucose oxidase (page 370).

The difference between the reference of Valdes et al. and the instant invention is that the reference of Valdes et al. does not teach a method of producing mutant glucose oxidase that is resistant to deactivation in the presence of peroxide. However, there are many methods widely available in the art of creating mutant genes by random mutations and screening for mutants displaying desired functional properties, such as having resistance to a chemical, such as a peroxide.

Cherry et al. (form PTO-892) discloses that wildype peroxidase is also deactivated in the presence of peroxide, a substrate for peroxidase, and solves this problem by making mutants of peroxidase that are resistant to deactivation in the presence of peroxide by using directed evolution techniques, both DNA shuffling and

error prone PCR, the same techniques used in the instant invention (abstract and pages 380-382). Cherry et al. discloses that multiple rounds of directed evolution yielded mutant peroxidases that are resistant to deactivation in the presence of hydrogen peroxide (pages 380-382). Cherry et al. discloses that colonies having enzymatic activity were selected to determine for its resistance against hydrogen peroxide (page 382).

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Hatzinikolaou et al. (form PTO-892) discloses a library of glucose oxidase genes known in the art, such as *A. Niger* (page 371). Hatzinikolaou et al. also discloses a method of isolating and purifying glucose oxidase as recited in claims 14-18 and methods of measuring glucose oxidase activity and concentration of glucose oxidase (pages 372-373).

Therefore, combining the teachings of Valdes et al., Cherry et al. and Hatzinikolaou et al., it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to apply the method of Cherry et al. to formulate or produce mutant glucose oxidases having resistance to peroxide by generating a library of mutated genes using the glucose oxidase gene of Hatzinikolaou et al., transforming *E. coli* with vectors comprising each of the mutated genes, growing colonies of said cells and determining whether the colonies have active glucose oxidase followed by determining whether the colonies or the glucose oxidase comprised in the colony are resistant to peroxide and then test for the functionality of the glucose oxidase in a glucose sensor. One of ordinary skill in the art would have been motivated to produce mutant peroxide resistant glucose oxidases in order to use them in glucose

sensors, thereby prolonging their use, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide, leading to failure of the sensor. One of ordinary skill in the art would have had a reasonable expectation of success since Hatzinikolaou et al. teaches glucose oxidase genes and Cherry et al. teaches a method of generating a library of mutant enzymes having resistance to hydrogen peroxide. Therefore, using the known technique of Cherry et al. to generate mutants of an enzyme having resistance against hydrogen peroxide would have been obvious to one of ordinary skill in the art.

Therefore, the above references render claims 1, 3-5, 12-15, 18-24 and 44-45 *prima facie* obvious.

Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Cherry et al. and Hatzinikolaou et al. as applied to claims, 1, 3-5, 12-15, 18-24 and 44-45 above, and further in view of MIXONIX.

Claims 16-17 are drawn to a method of formulating or producing mutant glucose oxidases, wherein colonies comprising said mutant glucose oxidase is disrupted via sonication.

Valdes et al., Cherry et al. and Hatzinikolaou et al. in combination teaches a method of formulating or producing mutant glucose oxidases, as discussed above.

The difference between the reference of Valdes et al., Cherry et al. and Hatzinikolaou et al. and the instant invention is that said references do not teach a method of disrupting cells via sonication.

However, disrupting cells via sonication, through the use of a sonicator, during protein purification is well known and routinely practiced in the art, see MISONIX (form PTO-892).

Therefore, combining the teachings of Valdes et al., Cherry et al. and Hatzinikolaou et al. and MISONIX, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to disrupt cells comprising mutant glucose oxidase via sonication. One of ordinary skill in the art would have been motivated to do so in order to disrupt cells comprising the mutant glucose oxidase. One of ordinary skill in the art would have had a reasonable expectation of success since disruption of cells using sonication is well known and practiced routinely in the art.

Therefore, the above references render claims 16-17 *prima facie* obvious.

Claims 6-8, 10-11 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Cherry et al. and Hatzinikolaou et al. as applied to claims 1, 3-5, 12-15, 18-24 and 44-45 above, and further in view of Wagner.

Claims 6-8, 10-11 and 46 are drawn to a method of formulating or producing mutant glucose oxidases by obtaining a library of glucose oxidase genes, creating a library of mutated glucose oxidase genes, introducing each mutated glucose oxidase

genes into separate expression vectors, inserting said vectors into host organisms, growing colonies of the host organism, determining whether the colonies contain active glucose oxidase by testing glucose oxidase in sensors and using fluorescence of a leuco-cryalsta-violet, and determining whether the colonies are resistant to peroxide.

Valdes et al., Cherry et al. and Hatzinikolaou et al. in combination teaches a method of formulating or producing mutant glucose oxidases, as discussed above.

The difference between the reference of Valdes et al., Cherry et al. and Hatzinikolaou et al. and the instant invention is that said references do not teach a method of determining whether the colonies contain active glucose oxidase by testing glucose oxidase in sensors and using fluorescence.

Wagner (EP 0 251 475 A1 - form PTO-892) discloses a method of determining glucose oxidase activity via a sensor by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission (pages 2-3). In the method of Wagner, the glucose oxidase is conjugated to a dye and immobilized in the sensor (page 3). Wagner also teaches that any fluorescent dye sensitive to quenching of its fluorescence emission by oxygen can be used (page 5).

Aldrich Catalog (cited previously on form PTO-892) discloses a leuco-cryalsta-violet dye (page 1005).

Therefore, combining the teachings of Valdes et al., Cherry et al. and Hatzinikolaou et al., Wagner and Aldrich Catalog, it would have been obvious to one

having ordinary skill in the art at the time the claimed invention was made to use the method of Wagner to ascertain activity of the glucose oxidase, wherein glucose oxidase is isolated and purified by the method taught by Hatzinikolaou et al. One of ordinary skill in the art would have been motivated to do so in order to determine whether the colonies comprising mutated glucose oxidases have active glucose oxidase. One of ordinary skill in the art would have had a reasonable expectation of success since Wagner teaches how to determine activity of glucose oxidase by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission.

Therefore, the above references render claims 6-8, 10-11 and 46 *prima facie* obvious.

(10) Response to Argument

Beginning at the top of p. 8 through middle of p. 9 of the Brief, appellant has summarized appellant's arguments.

Beginning at the middle of p. 9 of the Brief, appellant argues that the prior art of record does not teach or suggest the claimed invention because (1) Valdes et al. show that the direction taken by those skilled in the art was away from the method of the presently claimed invention, (2) Cherry et al.'s reference to peroxide resistance and inactivation conditions would not teach or suggest anything to one skilled in the art with regard to "creating a library of mutated glucose oxidase genes" because the goal of

Cherry et al. was to develop a dye-bleaching reagent in a clothes washing detergent and clothes washing environments is not suitable for production of glucose oxidase, and (3) Hatzinikolaou et al. does not teach formulating glucose oxidase enzyme by mutating glucose oxidases to make them resistant to peroxide degradation.

Appellant's arguments are not found persuasive.

(1) While it is true that Valdes et al. does not teach a method of producing a library of mutated glucose oxidase genes, Valdes et al. does teach that another option of addressing the peroxide degradation of glucose oxidase is to "prevent the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph). Contrary to applicant's argument that that the Examiner has quoted the above statement out of context to imply that Valdes et al. would have suggested a process involving creating mutated genes of glucose oxidase as claimed in the instant claims, Examiner is taking the position that one having ordinary skill in the art would have concluded that peroxide degradation of glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al., or to use other "techniques", such as generating glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as taught by Cherry et al.

Applicants also points out that Valdes et al. immediately follows the above statement with a description of the use of chemical additives as the so-called "better options" and therefore Valdes et al. teaches a specific direction (use of chemical additives) that departs from the conventional process of replacing a degraded enzyme

with a fresh enzyme. However, the absence of alternatives of a solution (i.e. mutant glucose oxidase resistant to peroxide degradation) does not criticize, discredit, or otherwise discourage the solution claimed. Since Valdes et al. does not teach that mutant glucose oxidase resistant to peroxide degradation is "undesirable", Valdes et al. does not teach away from the claimed method. See MPEP 2145, section D and *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

(2) In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The "goal" of Cherry et al. is irrelevant because the development of a dye-bleaching reagent using the mutant peroxidase of Cherry et al. is an intended use of said mutant peroxidase. The reference of Cherry et al. is relied upon for its teaching of a solution to the same problem disclosed by Valdes et al. Like glucose oxidase, peroxidase is also deactivated in the presence of peroxide. Cherry et al. provides a solution to this problem; a method of making mutants resistant to peroxide deactivation by using directed evolution techniques, both DNA shuffling and error prone PCR, the same techniques used in the instant claimed methods (abstract and pages 380-382).

(3) In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). The reference of Hatzinikolaou et al. is relied upon for its teaching of several glucose oxidase genes known in the art, such as *A. Niger* (page 371), from which a library of mutant glucose oxidase genes can be obtained by using the method of Cherry et al., and a method of isolating and purifying glucose oxidase as recited in claims 14-18 and methods of measuring glucose oxidase activity and concentration of glucose oxidase (pages 372-373).

Beginning at the middle of p. 14 of the Brief, appellant argues that the rejection is improper because prior art provides no motivation to combine and teaches away from the combination suggested by the Examiner because (1) Valdes et al. and other prior art teach away from the claimed method; (2) none of the cited prior art provide motivation to combine; and (3) without the present disclosure as a guide, one of ordinary skill in the art would not have arrived at the claimed invention.

Appellant's arguments are not found persuasive.

(1) As discussed above, Valdes et al. does teach that another option of addressing the peroxide degradation of glucose oxidase is to "prevent the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph). With this teaching at hand, one having ordinary skill in the art would have concluded that peroxide degradation of glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use other "techniques" known in the art, such as generating glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as

taught by Cherry et al. Valdes et al. does not teach away from a method of generating a library of mutant glucose oxidase genes because the absence of alternatives of a solution (i.e. mutant glucose oxidase resistant to peroxide degradation) does not criticize, discredit, or otherwise discourage the solution claimed. Since Valdes et al. does not teach that mutant glucose oxidase resistant to peroxide degradation is "undesirable", Valdes et al. does not teach away from the claimed method. See MPEP 2145, section D and *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

(2) "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw there from." (MPEP 2144). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art and the strongest rationale for combining references is a recognition, drawn from a convincing line of reasoning that some advantage would have been produced by their combination. In the instant case, Valdes et al. teaches that glucose oxidases in glucose sensors are deactivated by peroxide, leading to failure of the sensor, and techniques to "prevent the degradation of the enzyme" is advantageous. Cherry et al. teaches a technique to prevent degradation of an enzyme which is also degraded in the presence of peroxide; a method of making mutants resistant to peroxide deactivation by using directed evolution techniques, both DNA shuffling and error prone PCR, the same techniques used in the instant claimed methods (abstract and pages 380-

382). Therefore, one having ordinary skill in the art would have been motivated to combine the cited references in order to produce mutant glucose oxidases resistant to peroxide deactivation/degradation in order to use them in glucose sensors, thereby prolonging their use.

(3) It appears that appellant's are arguing that the examiner's conclusion of obviousness is based upon improper hindsight reasoning derived from appellant's specification. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, prior art teaches that glucose oxidase is degraded by hydrogen peroxide (Valdes et al.) and teaches that this problem can be addressed by preventing degradation of the enzyme. Cherry et al. teaches a method of making mutant enzymes having an advantageous predetermined property, such as resistance to a chemical, knowledge which was within the level of ordinary skill. Therefore, the motivations to combine the cited reference are not derived from appellant's own specification, but the motivation comes from the combined teachings of the cited references.

At the bottom of p. 21 of the Brief, appellant argues that each of the dependent claims 3-5, 10-15, 18, and 20-24 recite further features that distinguish those claims from the prior art. The instant rejection is not an anticipatory rejection. "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw there from." (MPEP 2144). It would have been obvious to one having ordinary skill in the art to create and screen/determine colonies for peroxide resistance as recited in claims 3-5 and 20-24 since Cherry et al. discloses a method of generating a library of mutant genes and screening for clones/colonies having the desired property. It would have been obvious to one having ordinary skill in the art to test glucose oxidase as recited in claims 10-11 since Wagner et al. discloses a method of determining glucose oxidase activity via a sensor. It would have been obvious to one having ordinary skill in the art to isolate glucose oxidase as recited in claims 12-15 and 18 since such isolation techniques are taught by Cherry et al. and Hatzinilolaou et al.

On bottom of p. 23 of the Brief, appellant argues that claims 16-17 are not obvious over Cherry et al., Hatzinikolaou et al. and further in view of MISONIX for the reasons discussed above.

Beginning at the top of p. 24, appellant argues that neither Wagner nor Aldrich Catalog would lead to the presently claimed invention since neither of the references teach nor suggest formulating a glucose oxidase enzyme by mutating glucose oxidase to make them resistant to peroxide degradation.

Appellant's arguments are not found persuasive.

The motivation to combine the cited references is to produce mutant peroxide resistant glucose oxidases in order to use them in glucose sensors, thereby prolonging their use, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide, leading to failure of the sensor, and Cherry et al. teaches a method of producing mutant enzymes that are resistant to peroxide degradation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Yong D Pak/

Primary Examiner, Art Unit 1652

Conferees:

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Supervisory Patent Examiner, Art Unit 1652

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